Remarks

Claim 16 is rejected under 35 USC § 103(a) as being obvious over Maeda et al. in view of Ward. The Examiner appears to rely on the fact that Maeda et al. looked at the ability of AHPP to lower uric acid as somehow meaning that Maeda et al. teach targeting uric acid. The fact that a xanthine oxidase inhibitor can cause a decrease in uric acid is not surprising. However, what Maeda never realizes or suggests is that uric acid levels produced by xanthine oxidase are causative of hypertension in addition to, or as opposed to, the oxidants produced by xanthine oxidase. Furthermore, it cannot be fairly said that the methods taught by Maeda et al. somehow necessarily achieves the uric acid levels as recited in claim 16. The Examiner theorizes that if one optimizes the dosages of AHPP then one will achieve the uric acid levels as recited in claim 16. Where is the proof of this? There are numerous possibilities and unknowns concerning the administration of AHPP and what might or might not happen upon administration of AHPP in humans. It is possible that a certain dosage may be appropriate for lowering oxidants but not uric acid. If the aim is to lower oxidants one might never realize the benefit of dosing for the purpose of lowering uric acid to certain levels. Applicants assert that when the Maeda patent is considered alongside other prior art, and in view of how experts interpreted the role of uric acid prior to Applicants' work, it becomes clear that targeting uric acid was not obvious (see further discussion below).

Applicants point out that the Patent Office is required to view the prior art as a whole and also to consider any objective evidence of nonobviousness submitted by Applicants and factor such evidence into the analysis of obviousness. "The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination." MPEP 2141. "Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103." MPEP 716.01(a) and MPEP 2141. Applicants submit herewith a Declaration from Dr. Rodriguez-Iturbe, President-Elect for the International

Society of Nephrology. Dr. Rodriguez-Iturbe has conducted extensive studies in the SHR rat and is a world expert in the field of high blood pressure and nephrology. Dr. Rodriquez-Iturbe states the following:

> Much of my research has focused on animal models of hypertension, including studies in the SHR rat[1-4]. This is a hereditary model of hypertension that we and others have shown is mediated by oxidative stress. While I am aware that xanthine oxidase inhibitors have been reported to lower blood pressure transiently in this model[5] (also the Maeda Patent U.S. Patent 5,747,495), none of those studies suggested that this was due to uric acid, but rather asserted that this was due to oxidative stress. In fact, uric acid is considered an antioxidant and in some recent pilot studies we can show that it can lower blood pressure in these animals. Furthermore, most of the studies documenting oxidative stress in models of hypertension have focused on the role of NADPH oxidase, either produced by vascular cells[6,7] or by the inflammatory cells themselves[1-4].

Dr. Rodriguez-Iturbe clarifies that Maeda et al. does not suggest that the transient lowering of blood pressure by AHPP is due to uric acid, but rather was due to oxidative stress. Dr. Rodriguez-Iturbe also points out that uric acid is considered an antioxidant and states that uric acid can even lower blood pressure in the SHR rat. This evidence certainly argues against lowering uric acid, and at a minimum, invalidates the interpretation of Maeda et al.'s SHR data as leading one to target uric acid to predefined levels.

Dr. Rodriguez-Iturbe goes on to state that the ultimate failure of xanthine oxidase inhibitors in hypertension studies in the SHR rat taught those skilled in the art away from using them for the treatment of hypertension:

> While x.o. inhibitors could have some effects on blood pressure via their antioxidant effects, the observation that they failed to lower BP in longterm studies in the SHR [9-11] <u>taught away those skilled in the art from using them in patients with hypertension</u>. Furthermore, as mentioned above, I believe that most of the oxidative stress in hypertension is due to a different system (NADPH oxidase) that is not inhibited by xanthine oxidase inhibitors. (emphasis added)

Dr. Rodriquez-Iturbe's statement above is corroborated by Dr. George Bakris as evidenced in the attached DECLARATION OF GEORGE BAKRIS, M.D. Dr. Bakris is a

Professor of Medicine and is the Director of the Hypertensive Diseases Center at the University of Chicago, Pritzker School of Medicine. Dr. Bakris is a recognized world expert in the field of high blood pressure is also a member and coauthor of the Joint National Committee 7 on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which provides the primary guidelines for blood pressure management in the United States. With respect to hypertension studies in the SHR, Dr. Bakris states the following:

> I am aware that there were earlier studies in which it was reported that xanthine oxidase inhibitors could lower blood pressure in the spontaneously hypertensive rat (SHR)[4]. The authors of the SHR studies always thought that the xanthine oxidase inhibitors were functioning as antioxidants since they block xanthine oxidase-generated oxidants. In particular, never was efficacy linked with targeting uric acid levels to certain ranges. Moreover, the concept that these agents might be useful to treat hypertension was thwarted by the fact that these inhibitors did not lower BP in longterm studies in the SHR[5-7]. Incidentally, it should be noted that antioxidants have largely failed in the treatment of hypertension[8]. (emphasis added)

Accordingly, Dr. Rodriguez-Iturbe and Dr. Bakris make clear that the studies in the SHR rat, such as those presented in the Maeda patent, ultimately lead those skilled in the art away from using xanthine oxidase inhibitors as a treatment for hypertension, and certainly did not suggest targeting uric acid to predetermined levels. To emphasize the point, Applicants provide the following quote from Dr. Rodriguez-Iturbe:

> I therefore conclude that the concept of lowering uric acid as a means to control blood pressure was a novel idea for which Dr Johnson brought forth the first direct experimental[8] as well as human[12] evidence. Studies in the SHR rat did not provide a reasonable expectation to those skilled in the art of successfully treating hypertension via administration of x.o. inhibitor, much less did they teach or suggest to those skilled in the art to use x.o. inhibitors as a means to lower blood pressure by reducing uric acid levels. Paragraph 3, Rodriguez-Iturbe Declaration (emphasis added).

Furthermore, after the documented failures in the SHR rat referenced by Dr. Rodriguez-Iturbe, other studies were published later that emphatically concluded that uric

acid is not causative and should not be controlled in the treatment of hypertension. As Dr. Bakris states, prior to Dr. Johnson's work "[T]he longstanding belief, based on studies such as the Framingham Heart Study[3], was that elevated uric acid in hypertension was a secondary phenomenon and not causative of hypertension. Moreover, the notion of prescribing medicines to lower uric acid for treating hypertension would have been considered, by experts in the field, as an improper and wasteful medical practice. As such, we did not list uric acid as a risk factor for hypertension in the JNC7 report, nor was this done by any other major society." (emphasis added).

The statements above from experts in the field of hypertension establish (1) that the prior art, when viewed as a whole, taught away from targeting uric acid, (2) that there was no expectation by those skilled in the art that lowering uric acid would lower blood pressure (and no motivation to do so), and (3) that there was skepticism by experts concerning whether lowering uric acid would work to lower blood pressure.

The establishment of a prima facie case of obviousness based on the cited Maeda patent requires some suggestion in the prior art to modify the teachings of the Maeda patent to somehow adjust the dosages of AHPP to lower uric acid so as to achieve a level of 4-6 mg/dl. As a fundamental fact issue, Applicants assert that such suggestion or motivation is not present in the prior art. As pointed above, the Maeda patent does not teach or suggest any dosages that would achieve the claimed uric acid levels. Whether one might stumble upon appropriate dosages in an optimization process is mere speculation, and not supported by any evidence. Moreover, the prior art specifically pertinent to uric acid taught that uric acid was irrelevant to hypertension and not to be measured. Thus, the prior art as a whole lacks a sufficient, reasonable, rational motivation for one skilled in the art to modify the Maeda patent in order to correlate specific dosages of AHPP to a specific uric acid level.

Furthermore, the Expert Declarations establish critical objective criteria that would rebut a prima facie case of obviousness. The Declarations make clear that more pertinent and more fully developed prior art relating to uric acid's relationship to

hypertension taught away from targeting uric acid. The Declarations establish there was skepticism by experts that lowering uric acid could effectively treat hypertension. At a minimum, the Declarations establish that there was a lack of expectation in the art that uric acid was causative and that administering uric acid lowering medicines could treat hypertension. Accordingly, to the extent that the Examiner believes that the Maeda patent establishes a prima facie case of obviousness, Applicants respectfully assert that the evidence of objective criteria of nonobviousness submitted herewith strongly rebuts obviousness.

Applicants point out that those skilled in the art would not interpret Ward as providing a reasonable motivation to modify the teachings of the Maeda patent to achieve uric acid levels of 4-6 mg/dl as a treatment of hypertension. Dr. Bakris, an expert in the field of hypertension, says this about the Ward reference:

> I have read the editorial published in 1998 by Ward[9] which is a mini-review of the theories concerning uric acid discussed in the literature at that time: some suggesting uric acid is a risk factor and some suggesting that uric acid is protective. The Ward paper does not assert either way whether uric acid is a risk factor or protective. The Ward paper clearly does not hypothesize nor suggest that uric acid plays a causative role in hypertension. It is important to understand that those skilled in the art of science and medicine are careful to not confuse something considered as a risk factor with something that is a causative factor. As an example, let's assume that a study finds that drinking alcohol is a risk factor associated with lung cancer. Those skilled in the art would not assume from this that drinking alcohol causes lung cancer (the medical community would undoubtedly interpret this study to mean that many people who drink also smoke). Likewise, when Ward or any similar paper in the literature prior to the Framingham Heart Study discussed the possibility of uric acid as being a risk factor for hypertension, this was not interpreted to mean that uric acid caused hypertension. The only way to determine whether drinking alcohol causes lung cancer or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study. The study conducted in the paper published by the Framingham Heart Study Group[3] was directly tailored to examine the same theories regarding uric acid that were discussed by Ward. As alluded to above, the Framingham Heart Study Group emphatically concluded that uric acid does not have a causative role in cardiovascular disease. Furthermore, prior to Dr Johnson's work there was no proposed mechanism(s) by which

> uric acid might cause hypertension. Accordingly, the Ward paper itself did not provide a motivation in the art to control uric acid levels as a means to control hypertension.

Based on the interpretation of Ward provided above by a world expert in hypertension, Applicants respectfully assert that Ward paper fails to cure the deficiencies of the Maeda patent. Ward does not provide the requisite motivation to modify the Maeda patent to achieve a method of treating hypertension by lowering uric acid to achieve a level of 4-6 mg/dl. In view of the foregoing remarks, and attached expert declarations, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103 rejection.

Next, claim 16 is rejected under 35 USC § 103(a) as being obvious over Baldwin et al. in view of Ward. Applicants respectfully traverse. The Examiner theorizes that if one optimizes the dosages of Baldwin compounds then one will achieve the uric acid levels as recited in claim 16. Applicants respectfully assert that this speculation is not supported by the Baldwin patent. There are numerous possibilities and unknowns concerning the administration of the experimental Baldwin compounds and what might or might not happen upon administration of them in humans. The Baldwin patent defines two different classes of compounds, ones that particularly work as hyperuricemic agents, Formula (I) and ones that particularly work as hypertensive agents (III). The fact that Baldwin teaches two different formulas that result in two different effects strongly suggests that there are two different mechanisms associated with the specific structures. Certain structures lower uric acid, while other structures are hypotensive.

In all of the teachings in the Baldwin patent, never is it taught or suggested that uric acid is causal of hypertension and that it is uric acid that must be targeted to control hypertension. Indeed, this is counterintuitive to the teachings of Baldwin. For example, Baldwin teaches away (or suggests away) from using a compound of Formula (I) (taught as being useful to lower uric acid) for testing as a compound to lower blood pressure, which are different compounds included under Formula (III). Furthermore, it cannot be suggested that the Baldwin reference is even enabling for the control of hypertension by

targeting specific levels of uric acid. Applicants respectfully assert that basing the rejection on the allegation that 'optimization' of Baldwin compounds would somehow result in achieving the uric acid levels recited in claim 16 for treating hypertension is unfair speculation.

Applicants respectfully point out that the Baldwin patent was issued in 1977. In 1999, experts declared that uric acid was irrelevant to hypertension (Framingham Study). Certainly, the over 22 year time period between the Baldwin Patent and the filing of the subject application, and the fact that the most pertinent prior art surrounding the filing date of the subject application declaring that uric acid should not be targeted, corroborated by the submitted Expert Testimony, must represent evidence that targeting specific uric acid levels was not obvious.

Thus, as a factual issue, Applicants assert that no reasonable motivation, supported by a rational underpinning, existed to modify the Baldwin patent to achieve all of the limitations of claim 16. This alone should serve to nullify a prima facie case of obviousness. Moreover, the objective evidence of nonobviousness presented above (teaching away by the prior art, skepticism by experts and absence of a reasonable expectation of success), rebuts a prima facie case of obviousness. Applicants respectfully assert that the evidence when viewed as a whole does not support a rejection of obviousness.

Ward is cited in conjunction with the Baldwin patent. Based on the interpretation of Ward provided above by a world expert in hypertension, Applicants respectfully assert that Ward paper fails to cure the deficiencies of the Baldwin patent. Ward does not provide the requisite motivation to modify the Baldwin patent to achieve a method of treating hypertension by lowering uric acid to achieve a level of 4-6 mg/dl. In view of the foregoing remarks, and attached expert declarations, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103 rejection.

Claims 16 and 17 are rejected under 35 USC § 103(a) as being obvious over Nakamoto in view of Ward. Applicants respectfully traverse. First, Applicants do acknowledge that Nakomoto does not teach or suggest achieving levels of 4 to 6 mg/dl to treat hypertension. However, Applicants object to the Patent Office's reliance on the flawed statement in Nakamoto for the allegation that Nakamoto teaches that compounds that lower uric acid are effective in treating hypertension. Applicants provide the comments of Dr. Richard Johnson, included in the attached SECOND DECLARATION OF RICHARD JOHNSON, M.D. (Dr. Johnson, in his own right, being an expert in the of hypertension), which show that the statement made in the Nakamoto patent relied on by the Examiner is so flawed that it would not be given any weight, and indeed was not given weight by those skilled in the art:

> 1. I have studied the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor. However, the Nakamoto patent makes one statement that the U.S. Patent Office relies on for its allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension[1]. Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, lines 55). This reasoning in the Nakamoto reference is so defective from a medical/scientific perspective that even a person with little skill in the art would immediately reject it. Those trained in science and medicine are careful not to confuse association with causation. The Nakamoto patent authors clearly make this mistake. As an example, let's assume that a study finds that smoking is associated with liver cirrhosis. Those skilled in the art would not conclude from this that smoking causes liver cirrhosis (rather the medical community would undoubtedly interpret this study to mean that many people who smoke also drink). The only way to determine whether smoking causes liver cirrhosis or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study. I note that Nakamoto provides <u>zero</u> supporting data or evidence to support its reasoning. Paragraph 1, Second Johnson Declaration.

The above quote from Dr. Johnson provides an explanation of how one skilled in the art would interpret the statement made in the Nakamoto patent that is relied on by the Examiner. Ultimately, this statement would be discounted outright and would not represent any credible teaching to those skilled in the art concerning whether uric acid should be targeted to control hypertension. In fact, the evidence surrounding the

Nakamoto patent reveals that the Nakamoto patent was never accepted by those skilled in the art as teaching a treatment of hypertension. As Dr. Johnson points out:

> To my knowledge, there have never been any clinical trials using the Nakamoto uricosuric compound. Had those skilled in the art thought that the Nakamoto uricosuric compound could cure or prevent hypertension by lowering uric acid, certainly there would have been studies to test the compound for this purpose or studies testing other known uricosurics. However, the scientific and patent literature reveals that the Nakamoto patent was not accepted as presenting a cure for hypertension, whether by administering its uricosuric compound or otherwise. A literature search in the PubMed database and a patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work. In contrast, members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note that the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension[2], such conclusion being supported by a comprehensive scientific study. Paragraph 2, Second Johnson Declaration.

The foregoing expert evidence shows that those skilled in the art did not consider the flawed statement of Nakamoto as representing a bona fide discovery that uric acid levels are causative of hypertension. As has been repeated throughout this response, those skilled in the art, and indeed experts in the art, believed that uric acid was merely associative and not causative. Thus, there would have been no motivation or suggestion in the prior art to target uric acid levels in an effort to treat hypertension. Furthermore, with respect to claim 17, there are additional reasons why the Nakamoto patent does not render obvious the implementation of allopurinol for treatment of hypertension. The cited Nakamoto patent makes statements which in actuality serve to teach away from administering allopurinol. In particular, the Nakamoto patent states that "Allopurinol, benzbromarone and probenecid have been clinically used, but they have various adverse effects and are not satisfactory. For example, allopurinol which is believed to inhibit formation of uric acid in the final stage of purine metabolism causes efflorescence, gastrointestinal disorders, liver troubles and hematogenic organ troubles and involves a risk of having bad influences on other metabolic systems." Nakamoto patent, page 2, lines 15-17. In the name of fairness, this statement would not reasonably lead one skilled in the art to use allopurinol for any purpose, much less for treating hypertension. No

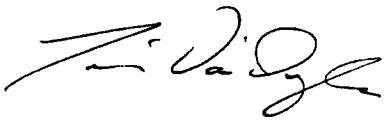
suggestion of using allopurinol for treating hypertension has been provided in any of the prior art.

For the similar reasons provided above, the Ward reference does not cure the deficiencies of the Nakamoto patent. To quote Dr. Rodriguez-Iturbe: "The Ward paper does not assert either way whether uric acid is a risk factor or protective. The Ward paper clearly does not hypothesize nor suggest that uric acid plays a causative role in hypertension." It cannot be reasonably said that Ward provides a motivation to modify the Nakamoto patent. Applicants ask the Examiner to not forget that the Nakamoto patent says nothing about the administration of a xanthine oxidase for any purpose, other than its reference to allopurinol. It says that allopurinol is not satisfactory as a means to lower uric acid and states several adverse effects of allopurinol. Thus, a combination of Nakamoto with Ward, does not legitimately teach all of the limitations of claim 16 and 17. Such combination of references does not result in a motivation to administer xanthine oxidase inhibitors, and much less does it teach administering xanthine oxidase inhibitors to achieve the target levels of uric acid recited in claims 16 and 17. Accordingly, in view of the foregoing remarks, and attached expert declarations, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103 rejection.

Lastly, claim 18 is rejected under 35 USC § 103(a) as being obvious over Nakamoto. Applicants respectfully traverse. The office action states that Nakamoto et al. discloses a method of lowering uric acid comprising a xanthine oxidase inhibitor, allopurinol. As stated above, Nakamoto's discussion actuality teaches away from administering allopurinol. "Allopurinol, benzbromarone and probenecid have been clinically used, but they have various adverse effects and are not satisfactory." Nakamoto patent, page 2, lines 15-17. In addition, Applicants have provided support concerning the interpretation of the Nakamoto's statement concerning gout and hypertension. The Nakamoto patent makes a statement that clearly confuses association with causation, and which was given no weight by experts in the field. Thus, Applicants assert that the Nakamoto patent does not suggest a treatment for hypertension. Certainly it cannot be said that Nakamoto suggests the administration of allopurinol for treating hypertension,

when the only mention of allopurinol by the Nakamoto patent is that allopurinol has various adverse effects and is an unsatisfactory compound. Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103 rejection.

Respectfully submitted,



Timothy H. Van Dyke
Reg. No. 43,218
Beusse Wolter Sanks Mora & Maire, P.A.
390 N. Orange Avenue, Suite 2500
Orlando, FL 32801
(407) 926-7726